

EDITORIALS

Transient Apical Ballooning Syndrome: a Transition Towards Adulthood

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The seeds of the concept of aneurysm or reversible acute ballooning of the left ventricular apex were sown in a number of papers written in Japan in the early nineties. However, it is true to say that the birth of transient apical dysfunction syndrome (TADS) of the left ventricle as an independent clinical entity came in July 2001 with the publication of a series of 88 Japanese patients by Tsuchihashi et al.¹ Since then, many new cases have been described, the majority of which also come from Japan.^{2,3} Later, these were followed by series of patients diagnosed in other countries, which confirmed that the incidence of TADS is not restricted to specific ethnic groups and geographical areas.^{4,5} Cases have also been described in Spain^{6,7} and in the current issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA, Ibáñez et al⁸ report on a series of an appreciable size given that the disorder is rare in Spain, with an incidence of only 0.5%-1% in patients admitted with suspected acute myocardial infarction (AMI).

Analysis of these series enables us to distinguish the characteristics of TADS. The disorder occurs mainly in women (over 80% of patients) of an advanced age (median >70 years; occasionally <50 years), and is frequently triggered by physical or emotional stress. TADS presents with symptoms similar to AMI but with slight differences: chest pain is present in the majority of patients but is not always typical, and is of slight to moderate intensity. Electrocardiographic (ECG) studies reveal ST segment elevation on the anterior surface in 90% of patients and this is usually more marked in V4-V6 than V1-V3, which contrasts with typical cases of AMI. In one in four patients, we find Q waves that disappear after the acute phase. Almost all patients present negative T waves from the second day, which are conspicuous in the precordial leads, together with a prolonged QTc interval. These

ECG anomalies are transient, although T wave alterations can last longer. Enzyme elevation is disproportionately lower than the ECG changes might suggest and does not occur in almost half of the patients.⁸

This disorder is defined by a characteristic form of left ventricular dysfunction with hypokinesia, akinesia, or dyskinesia of apical segments, and hypercontractility of baseline segments. These features are observed during the acute phase and usually return to normal between 1 and 3 weeks later although in isolated cases this can be delayed by up to 2 months. In most patients, the shape of the ventricle is determined by angiography although non-invasive observation of the characteristic morphology by methods such as echocardiography is equally valid, as Ibáñez et al demonstrate.⁸ Early catheterization usually shows normal coronary arteries although several series include patients with non-significant lesions. Some authors believe the absence of early angiography complicates diagnosis^{1,2} whereas others accept that studies can be performed at a later point.^{4,7} Other series include patients who have not undergone angiography at all.^{3,5}

After the birth and infancy of TADS, so to speak, the entity could currently be said to be in full adolescence, characterized by the controversies and contradictions typical of its age. The two principal areas of uncertainty that contribute to TADS' immaturity are the diagnosis of the disorder and its etiology. Clarification of both will lead to substantial advances in practical management of the illness.

DIAGNOSIS OF TRANSIENT APICAL DYSFUNCTION

Criteria used to define TADS differ greatly in the series published. Practical implications of diagnosis are important as the differences between TADS and AMI (neither obstructive coronary lesions nor intraluminal thrombus have been found in TADS) mean therapeutic options such as fibrinolysis, heparinization or the administration of IIB-IIIa plaque receptor antagonists are both unnecessary and potentially dangerous. This is also the case with chronic treatments aimed at preventing destabilization of atherosclerotic

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plaque such as the use of antiplatelet and lipid-lowering drugs.

Moreover, correct diagnosis of TADS has consequences for prognosis. In spite of frequent acute phase complications, mortality is extremely low in comparison with AMI-related mortality during hospitalization (<2% of all patients) and during follow-up (only one of 87 patients with TADS died during the average 13 months follow-up in the principal series).¹

Consequently, we need to obtain a consensus definition of TADS that is practical and applicable. Conscious of this, in their recent review of the entity Abe and Kondo⁹ propose a list of diagnostic criteria (major, minor and exclusion) to facilitate recognition of the disorder. Unfortunately, their efforts are incomplete as the list does not refer to the role of coronary angiography. They also use some highly unspecific diagnostic criteria such as “chest pain,” “ST-T segment abnormalities,” or “limited elevation of cardiac enzyme.” Furthermore, they offer no guidance as to how criteria should be applied.

An ideal system for the diagnosis of TADS would have several qualities, among others: *a*) consensus on the criteria used by various authors; *b*) the ability to distinguish TADS from similar entities such as AMI; *c*) easy applicability, by including the lowest possible number of criteria together with clear definitions, and *d*) usable in the acute phase of the disorder and in patients analyzed *a posteriori*, and sensitive enough to diagnose patients who do not undergo angiographic studies during the acute phase.

In Table , we propose a diagnostic method based on several of these characteristics. Before we evaluate the criteria, two conditions must be met. First, we have to consider the identification of the transient apical dysfunction which gives its name to the disorder. Non-invasive methods, such as echocardiography, resonance imaging or isotope ventriculography, should be used if the images obtained are of adequate quality. We also need to discount other causes of reversible contractile dysfunction of the left ventricle, such as subarachnoid hemorrhage, pheochromocytoma, myocarditis, myocardial stunning due to cardiac ischemia, acute effects of cocaine or other toxic substances, etc.

Coronary angiography plays a central role in diagnosing TADS. Ideally, it is performed during the acute phase (within 24 h of the onset of the disorder) and shows anatomically normal coronary arteries. This would be a major criterion and sufficient in itself as a diagnosis of TADS. In patients whose early angiogram shows non-significant lesions (lesions causing stenosis <50% without apparently complicated plaque or thrombus) or who undergo late angiography (between the second and seventh day after the onset of symptoms) and show non-significant lesions, evidence indicating TADS is less convincing. Consequently, we need to identify another clinical criterion typical of the

TABLE. Diagnosis of Transient Apical Dysfunction Syndrome*

Prior conditions (both obligatory):

Evidence of transient apical dysfunction of left ventricle with a typical shape in the systole (rounded apex and narrow “neck” due to hypercontractility of baseline segments), diagnosed by angiography, echocardiography, isotopes, or cardiac magnetic resonance. Typically, normal ventricular mobility returns in 2-3 weeks although data exist showing it may take up to 2 months

Absence of other conditions associated with transient regional systolic dysfunction of the left ventricle: subarachnoid hemorrhage, pheochromocytoma, myocardial stunning due to cardiac ischemia, effects of toxic substances (cocaine), myocarditis, etc

Diagnostic Criteria

Major criteria

Early coronary angiography (first 24 h) without anatomical lesions

Minor criteria

1. Early coronary angiography with non-significant lesions (<50% without characteristics of complicated plaque or intraluminal thrombus)
2. Late coronary angiography (between 2 and 7 days after the onset of symptoms) without significant lesions
3. Disorder triggered by physical or emotional stress
4. Typical ECG changes
 - ST segment elevation in acute phase, more marked in V4-V6 than in V1-V3
 - Appearance of Q waves that disappear after acute phase
 - Negative T waves very prominent in V1-V6
 - Prolongation of QTc
5. Woman aged >50 years

Confirmed TADS: major criterion or 2 or more minor criteria, including one angiographic criterion

Probable TADS: 2 or more minor criteria, without including any of the angiographic criteria

*TADS indicates transient apical dysfunction syndrome.

disorder to confirm diagnosis. In the few cases of suspected TADS when an angiogram has not been performed, the presence of 2 clinical or electrocardiographic characteristics typical of the disorder would enable us to diagnose “probable TADS” rather than “confirmed TADS”, which would only be applied on the basis of angiographic findings. In order to achieve maximum discrimination, minor criteria are those that are common in patients with TADS but infrequent in classical AMI.

ETIOLOGY OF TRANSIENT APICAL DYSFUNCTION SYNDROME

This is probably the most controversial aspect of the entity. Only the identification of the underlying cause of the disorder will enable us to apply a rational treat-

ment but unfortunately we still do not know its etiology. Various hypotheses have been put forward and we will briefly review their relative merits now.

According to the nervous system theory, apical region dysfunction is determined by acute hyperactivity of the local sympathetic system. This hypothesis seems to be supported by the incidence of physical or emotional stress in all series as a proven, frequent, important trigger of TADS. (Data from more recent series is more accessible than that from older series.¹⁻⁴) Moreover, there are clear similarities between TADS and myocardial stunning due to the discharge of catecholamines present in subarachnoid hemorrhage or pheochromocytoma crisis. A more definitive argument is the recent description of an experimental model of TADS in rats in which continued stress provokes hypokinesia in the anteroapical region of the left ventricle.¹⁰ Despite the undoubted weight of these data, the evidence is not definitive: raised catecholamine concentration in the apical myocardium in the acute phase of TADS has not been proven. Nor do we know why the dysfunction only affects this segment when sympathetic nervous activity affects all of the myocardium. A slightly raised catecholamine level in peripheral blood has been found,² but this is non-specific and frequent in patients with a variety of acute illnesses.

The hypothesis that spasm of the epicardial coronary arteries (either all of them simultaneously or just one of them) might be the cause of TADS has been proposed since the first descriptions of the disorder in the early nineties, due to the coincidence of coronary spasm and myocardial stunning in isolated cases. However, early angiograms in TADS show the presence of spontaneous spasm very occasionally and test provocation with ergonovine or acetylcholine is only positive in 15%-30% of patients. Moreover, there are isolated descriptions of TADS starting during angiography with no spasm observed but, rather, a transient slowing of flow without changes in artery dimensions. This explains the hypothesis that microcirculatory spasm might be the underlying cause of disorder. However, when Abe et al³ sought to confirm this mechanism using prospective intracoronary Doppler in the acute phase, they did not find significant alterations.^{3,9} These authors, who demonstrated a reduction of the metabolism and mitochondrial function of the apical myocardium in the acute phase by using isotopes, suggest damage is produced by direct myocardial toxicity and not cardiac ischemia.

Some authors, such as Barriales et al,⁷ believe the appearance of an intraventricular gradient plays an important part in the development of TADS. They hypothesize that certain acute factors (adrenergic discharge, hypovolemia or ischemic heart disease among others) that act on ventricles with an unusual geometry (reduced cavity, sigmoid septum or narrow ventricular outflow tract) condition the appearance of an intraventricular

gradient. This would create a high pressure apical chamber in the walls of which ischemic phenomena are produced due to the increase in wall pressure and a reduction in myocardial perfusion that would finally cause apical contractile dysfunction. Should this theory be confirmed, treatment of TADS would be based on the management of volume and beta blocking agents or alpha sympathetic agonists, which has already been carried out successfully in isolated cases¹¹ as in patients with AMI with this complication.¹² The fundamental objection to this hypothesis lies in the absence of intraventricular gradient in the majority of patients with TADS in whom this factor was specifically studied prospectively.^{1,3}

Ibáñez et al⁸ contribute original data on the coronary artery anatomy of patients with TADS. The finding that all patients have a long course of the left anterior descending artery which extends to the inferior surface of the left ventricle is noteworthy, given that the inferior recurrent artery is usually less developed in the population at large. This suggests that coronary artery anatomy in the apical region may indicate an underlying predisposition to TADS. Thus far, the hypothesis is attractive, although it does not coincide with observations of other authors who specifically comment that the dysfunctional apical region in all patients extends along the territory of more than one coronary artery,² or that the anterior descending artery does not reach the apex in some patients with TADS.⁴ Based on this unusual anatomical finding, the authors consider that the pathogenesis of the disorder is similar to that of AMI: coronary atherosclerotic plaque complicated by thrombotic occlusion. The difference between TADS and classical AMI lies only in the shorter duration of the coronary artery occlusion in TADS, which explains why neither obstructive lesions nor intracoronary thrombus have been found in early catheterization. Evidence supporting the hypothesis is weak and hardly explains characteristics of TADS that differ greatly from atherosclerosis-related AMI. These include factors such as the greater presence of women among the population affected; the low profile of cardiovascular risk; the physical or emotional stress that triggers the disorder; the fact that the symptoms, evolution of the ECG results and enzyme curve atypical of AMI; the systematic absence of findings in early angiograms; and the apical myocardium histology without cellular necrosis. *A priori*, a syndrome such as TADS, which is usually followed by *restitutio ad integrum* of the affected heart, seems less likely to be due to transient physiological anomalies than to structural abnormalities of the artery wall or ventricle.

In the final instance, we do not know what causes TADS. Several of the mechanisms proposed may act in combination or in sequence and it seems likely that the initial catecholaminergic discharge may set off other mechanisms, such as macrovascular or microvas-

cular spasm or induction of intracavitary gradient, and others.

Without a doubt, early identification of patients with TADS together with the development of experimental models of the illness will enable us to disentangle its development mechanisms. Then, TADS will come of age, and treatment and efficient prevention will be available for patients affected by a disorder whose progress in modern cardiology has been as brief as it has been interesting.

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